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Applicant : David J. Pinsky
Serial No. : 09/374,586 Examiner: C. Stroup
Filed : August 13, 1999 Art Unit: 1633
For : CD39/ECTO-ADPASE AS A TREATMENT FOR
THROMBOTIC AND ISCHEMIC DISORDERS

1185 Avenue of the Americas
New York, New York 10036
June 6, 2000

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with his duty of disclosure under 37 C.F.R. §1.56, applicant would like to direct the Examiner's attention to the following disclosures, which are listed on Form PTO-1449 (**Exhibit A**). Copies of the disclosures listed below as items 1-35 are attached hereto as **Exhibits 1-35**, respectively.

1. Bowie E. J. W., et al., (1974) "The Bleeding Time", Progress in Hemostasis and Thrombosis, Spaet TH (ed) 2d Ed, New York, Grune & Statton, pp. 249-271 (**Exhibit 1**);
2. Broekmann, M. J., et al., (1991) "Inhibition of human Platelet Reactivity by Endothelium-Derived Relaxing Factor From Human Umbilical Vein Endothelial Cells in Suspension: Blockade of Aggregation and Secretion by an Aspirin-Insensitive Mechanism", Blood, 78: 1033-1040 (**Exhibit 2**);
3. Bronner, L. L., et al., (1995) "Primary prevention of stroke", N. Engl. J. Med., 333(21): 1392-1400 (**Exhibit 3**);
4. Buchanan M. R., et al., (1995) "Individual variation in the

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effects of ASA on platelet function: Implication for the use of ASA clinically", Canadian J. Medicine, 11(3):221-227 (Exhibit 4);

5. Steering Committee, Lancet., (1996) "A randomised, blinded, trial of clopidogrol versus aspirin in patients at risk of ischaemic events", CAPRIE 348: 1329-1339 (Exhibit 5);
6. Chiu, D., et al., (1998) "Intravenous tissue plasminogen activator for acute ischemic stroke: feasibility, safety, and efficacy in the first year of clinical practice", Stroke, 29: 18-22 (Exhibit 6);
7. Choudhri, T. F., et al., (1997) "Use of a spectrophotometric hemoglobin assay to objectively quantify intracerebral hemorrhage in mice", Stroke, 28: 2296-2302 (Exhibit 7);
8. Choudhri, T. F., et al., (1998) "Reduced microvascular thrombosis and improved outcome in acute murine stroke by inhibiting GP IIb/IIIa receptor-mediated platelet aggregation", J. Clin. Invest., 102: 1301-1310 (Exhibit 8);
9. Connolly, E. S. Jr., et al., (1996) "Cerebral protection in homozygous null ICAM-1 mice after middle cerebral artery occlusion. Role of neutrophil adhesion in the pathogenesis of stroke", J. Clin. Invest., 97: 209-216 (Exhibit 9);
10. Connolly, E. S. Jr., et al., (1997) "Exacerbation of cerebral injury in mice which express the P-selectin gene: identification of P-selectin blockade as a new target for the treatment of stroke", Circ. Res., 81: 304-310 (Exhibit 10);
11. Connolly, E. S. Jr., et al., (1996) "Procedural and strain-

related variables significantly affect outcome in a murine model of focal cerebral ischemia", Neurosurg., 38(3): 523-532 (Exhibit 11);

12. Dippel, D., (1998) "The results of CAPRIE, IST, and CAST", Thrombosis Res., 92: S13-S16 (Exhibit 12); ✓
13. Eitzman D. T., (1996) "Bleomycin-induced pulmonary fibrosis in transgenic mice that either lack or overexpress the murine plasminogen activator inhibitor-I gene", J. Clin. Invest., 97:232-237 (Exhibit 13);
14. Erickson, L. A., et al., (1990) "Development of venous occlusions in mice transgenic for the plasminogen activator inhibitor-I gene", Nature, 346: 74-76 (Exhibit 14);
15. Gayle, R. B., et al., (1998) "Inhibition of platelet function by recombinant soluble ecto-ADPase/CD39", J. Clin. Invest., 101: 1851-1859 (Exhibit 15);
16. Grotenmeyer, K. H., (1991) "Effects of acetylsalicylic acid in stroke patients; evidence of nonresponders in a subpopulation of treated patients", Thrombosis Res., 63: 587-593 (Exhibit 16);
17. Handa, M. & Guidotti, G., (1996) "Purification and Cloning of a Soluble ATP-Diphosphohydrolase (Apyrase) from Potato Tubers (*Solanum tubersum*)" Biochem. Biophys. Res. Commun., 218: 916-923 (Exhibit 17);
18. Harbison, J. W., (1998) "Clinical considerations in selecting antiplatelet therapy in cerebrovascular disease" Am. J. Health Syst. Pharm., 55: S17-S20 (Exhibit 18);

19. Hechler, B., et al., (1998) "The P2Y₁ receptor, necessary but not sufficient to support full ADP-induced platelet aggregation, is not the target of the drug clopidogrel", Br. J. Haematol., 103: 858-866 (Exhibit 19);
20. Huang, Z., et al. (1994) "Effects of Cerebral Ischemia in Mice Deficient Neuronal Nitric Oxide Synthase", Science, 265: 1883-1885 (Exhibit 20);
21. Koch, R. (1891) Verhandlungen des X. Internationalen Medizinischen Congresses Berlin 1: 35-47 (Abstract) (Exhibit 21)
22. Lawson C. A., et al., (1997) "Monocytes and tissue factor promote thrombosis in a murine model of oxygen deprivation", J. Clin. Invest., 99: 1729-1738 (Exhibit 22);
23. Maeda K, et al., (1998) "Differences in the cerebrovascular anatomy of C57black/6 and SV129 mice", Neuroreport, 9(7):1317-1319 (Exhibit 23);
24. Majid A., et al., (1999) "Intrinsic, hemodynamic-independent differences in vulnerability to permanent focal cerebral ischemia in common mutant mouse strains", 24th American Heart Association International Conference on Stroke and Cerebral CXJO-XXPY (Exhibit 24);
25. Maliszewski, C. R., et al., (1994) "The CD39 lymphoid cell activation antigen: Molecular cloning and structural characterization", J. Immunol., 153: 3574-3583 (Exhibit 25);
26. Marcus, A. J., & Safeir, L. B., (1993) "Thromboregulation:

- multicellular modulation of platelet reactivity in hemostasis and thrombosis", FASEB J., 7: 516-522 (Exhibit 26);
27. Marcus, A. J., (1999) "Platelets: Their role in hemostasis, thrombosis, and inflammation", In Inflammation: Basic Principles and Clinical Correlates (EDS Gallin, J.I. & Snyderman, R., Lippincott, Williams & Wilkins, Philadelphia: 77-95 (Exhibit 27);
28. Marcus, A. J., et al., (1997) "The endothelial cell ecto-ADPase responsible for inhibition of platelet function is CD39", J. Clin. Invest., 99: 1351-1360 (Exhibit 28); ✓
29. Marcus, A. J., et al., (1991) "Inhibition of platelet function by an aspirin-insensitive endothelial cell ADPase", J. Clin. Invest., 88: 1690-1696 (Exhibit 29);
30. Mayadas, T. N., et al., (1993) "Leukocyte rolling and extravasation are severely compromised in P-selection deficient mice", Cell, 74(3): 541-554 (Exhibit 30);
31. Mizutani H, et al., (1990) "Analyses of thrombocytopenia in idiopathic thrombocytopenic purpura-prone mice by platelet experiments between (NZW X BXSB)F₁ and normal mice", Blood, 75:1809-1912 (Exhibit 31);
32. Naka, Y., et al., (1995) "Enhanced preservation of orthotopically transplanted rat lungs by nitroglycerin but not hydralazine: Requirement for graft vascular homeostasis beyond harvest vasodilation", Circ. Res., 76: 900-906 (Exhibit 32);
33. Schoenborn, M. A., et al., (1998) "Gene structure and

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chromosome location of mouse Cd39 coding for an ecto-
apyrase", Cytogen Cell Gen., 81(3-4): 287-280 (Exhibit 33);

34. Wardlaw, J. M., et al., (1997) "Systematic review of
evidence on thrombolytic therapy for acute ischemic stroke
[see comments]", Lancet., 350: 607-614 (Exhibit 34); and
35. Wang, T. F., & Guidotti, G., (1996) "CD39 is an Ecto-
(Ca²⁺, Mg²⁺)-apyrase", J. Biol. Chem., 271, 9898-9901 (Exhibit
35).

Applicant requests that the Examiner review the references and
make them of record in the subject application.

No fee other than the \$240.00 Information Disclosure Statement
fee is deemed necessary in connection with the filing of this
Information Disclosure Statement. If any additional fee is
required, authorization is hereby given to charge the amount of
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Respectfully submitted,

Jane M. Love

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